Toward Early Pharmacological Posttraumatic Stress Intervention

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In the acute aftermath of exposure to extreme stress, nearly all trauma survivors experience one or more transient symptoms of stress. In the short run, these symptoms may serve an adaptive role and generally remit; in some cases, however, acute stress-related symptoms do not diminish and instead evolve into posttraumatic stress disorder (PTSD). At present it is not clear when and with whom to intervene. On one hand, it is possible that some responses, such as early intrusive memories, effectively recruit support from others and facilitate the psychological processing of trauma; on the other hand, failing to intervene clinically with a recently traumatized individual may permit the subsequent development of PTSD. In this review, we focus on potential pharmacologic interventions aimed at treating early symptoms of extreme arousal or dissociation with the hope of possibly preventing PTSD. To date there is almost no empirical data on effective pharmacologic interventions in the immediate aftermath of extreme psychological trauma. As a result, much of what is discussed in this review is speculative in nature Biol Psychiatry 2003;53:834–843 © *2003 Society of Biological Psychiatry*

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Introduction

In the acute aftermath of exposure to extreme stress, nearly all trauma survivors experience one or more transient symptoms, including hyperarousal, agitation, insomnia, dissociation, exaggerated startle, intrusive memories, and nightmares (Shalev et al 1998). In the short run, these symptoms may serve an adaptive role and generally remit on their own within a relatively brief period of time; in some cases, however, acute stress-related symptoms do not diminish and instead evolve into posttraumatic stress disorder (PTSD).

For clinicians working with recent trauma survivors, the prevention of PTSD is of utmost importance, but when and with whom to intervene is currently not well understood. On one hand, it is possible that some responses, such as early intrusive memories, effectively recruit support from others and facilitate the psychological processing of trauma (Shalev 2002). To intervene prematurely and abort these "adaptive" processes might actually prove harmful. On the other hand, failing to clinically intervene with a recently traumatized individual, who then goes on to develop PTSD, or intervening in a manner that proves harmful (Bisson et al 1997) would constitute a tragic and unnecessary mistake.

In recent years, investigators have begun to study early responses to trauma as predictors of subsequent PTSD. In general, survivors who do not develop early trauma-related symptoms do not develop PTSD (Shalev 2002). For survivors who do express early trauma-related symptoms, some, but not all, will later suffer from PTSD. Early symptoms that have been predictive of later PTSD include excessive arousal and fear (Brewin et al 1999; Bryant et al 2000; Harvey and Bryant 1998), peritraumatic dissociation (Bremner et al 1992; Koopman et al 1994; Marmar et al 1999), and depression (Feedman et al 1999; Shalev et al 1998). It is believed that treating these early predictive symptoms might lessen the likelihood of developing PTSD.

In this review, we focus on potential pharmacologic interventions aimed at treating early symptoms of extreme arousal or dissociation with the hope of possibly preventing PTSD. To date there is almost no empirical data on effective pharmacologic interventions in the immediate aftermath of extreme psychological trauma. As a result much of what is discussed in this review will be speculative in nature.

Exaggerated Arousal and Enhanced Memory for Traumatic Events

Multiple cortical and subcortical brain regions (including sensory, motor, prefrontal and cingulate cortex, hippocampus, amygdala, thalamus, striatum, midbrain, and brain stem monoaminergic nuclei and hypothalamus) become activated during stress. Communication between these regions facilitates evaluation of, psychomotor response to, and memory for stress-related events and is highly dependent on glutama-

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tergic signaling. For example, glutamate is critically involved in conveyance of sensory information from periphery to thalamus; from thalamus to amygdala, hippocampus, and cortex; and from amygdala, hippocampus, and cortex back to thalamus (Chambers et al 1999; Krystal et al 1995).

Glutamate, an amino acid, is the brain's primary excitatory neurotransmitter. It subserves nearly all fast excitatory point-to-point synaptic transmission in the brain and is rapidly released in response to arousing and dangerous situations. During resting nonstressful states, excitatory glutamatergic synaptic transmission is regulated by γ-aminobutyric acid (GABA), the brain's primary inhibitory neurotransmitter. Tonic inhibition by GABA, in multiple brain regions such as the thalamus and amygdala, allows the brain to filter out a continuous flow of irrelevant and extraneous sensory information; however, during stressful or dangerous situations when excitation is increased, elevated levels of glutamate are able to overcome tonic inhibition by GABA and thereby trigger a cascade of protective responses (Krystal et al 1995).

Although stress-induced elevations of glutamate serve to mediate cortical and subcortical communication and responses to stress, failure to regulate and modulate heightened glutamatergic activation can lead to extreme changes in intracellular calcium, toxicity, and even cell death (Armanini et al 1990; Stein-Behrens et al 1994; Thomas 1995). To protect the brain from its own excitation, additional GABA is released during stress. Thus, in addition to providing tonic inhibition to multiple brain regions during nonstressful states, increased GABAergic inhibition during stress helps to contain and terminate excitation, which if left unchecked could be disorganizing and toxic.

The balance between excitatory and inhibitory processes that facilitate a coherent exchange of information within cortical-limbic networks depends not only on glutamate and GABA interactions but also on a host of modulators (peptides, monoamines, and hormones). For example, during arousing or dangerous situations, midbrain sources of dopamine (ventral tegmental area, substantial nigra) modulate aspects of frontal executive and motor cortex responsiveness, whereas noradrenergic (locus ceruleus) and serotonergic (raphe nucleus) projections to cortex, thalamus, amygdala, and hippocampus influence stress-related perceptual and memory processes. In contrast to the fast-acting effects of glutamate and GABA, modulators act more slowly and primarily exert their influence by augmenting or inhibiting the effects of these faster acting transmitters (Chambers et al 1999; Charney et al 1995).

Attention, arousal, and fear-related behaviors are critical for survival; however, it has been hypothesized that excessive and sustained arousal, following exposure to trauma, may increase the likelihood of developing PTSD (Brewin et al 1999; Bryant et al 1999; Harvey et al 1998). Preclinical investigations have demonstrated that augmented or extended states of alarm facilitate the onset of stress sensitization and long-term potentiation, both of which may contribute to the underlying pathophysiology of PTSD (Blank et al 2002). Compatible clinical data have shown that excessive arousal in survivors during the first several weeks after trauma predicts the later development of PTSD (Brewin et al 1999; Bryant et al 2000; Harvey et al 1998). Based on these observations, one might expect that reducing excessive arousal within the first several weeks of a trauma would decrease the likelihood of developing PTSD.

Reducing arousal requires a rebalancing of excitatory and inhibitory brain processes. There are numerous potential routes to achieve this goal, all of which eventually result in the inhibition or modulation of central nervous system (CNS) excitatory glutamatergic systems. In this discussion of arousal, we have chosen to focus on potential pharmacologic approaches to treating noradrenergic hyperreactivity because this system is central to fear and arousal and because it is one of the most thoroughly studied neurobiologic systems in clinical studies of PTSD. It is important to emphasize that the noradrenergic system represents only one element in the complex array of neurobiological systems that determine overall level of arousal and attention.

Noradrenergic Systems: Arousal and Memory

Central noradrenergic neurons serve as elements within a diffuse modulatory system (Zigmond et al 1995) that detects and responds to meaningful internal and external stimuli. A discrete group of hindbrain nuclei, the most prominent of which is the locus coeruleus (LC), contains the cell bodies of most noradrenergic neurons in the brain. The locus coeruleus processes relevant sensory information through its diverse afferent inputs and has an efferent network that can potentially facilitate anxiety and fear-related skeletal motor, cardiovascular, neuroendocrine, and cognitive responses. Electrical and pharmacologic stimulation of the LC elicits fear-related behaviors (in primates) and increased release of norepinephrine (NE) in multiple brain regions, such as the amygdala, hippocampus, and prefrontal cortex. These brain regions are involved in perceiving, evaluating, remembering, and responding to potentially threatening stimuli. Bilateral lesions of the LC dramatically reduce fear behaviors and NE release in threatening situations (Charney et al 1995; Redmond 1987).

A large body of preclinical evidence suggests that central noradrenergic nuclei play a critical role in the level of alertness, vigilance, orienting to novel stimuli, selective attention, and cardiovascular responses to life-threatening stimuli (Aston-Jones et al 1994). NE also plays a central role in the encoding and enhanced consolidation of memory for events that are arousing, stressful, or fear provoking. Although multiple other stress-induced neuromodulators, such as epinephrine, glucocorticoids, opioid peptides, GABA, and glucose also effect consolidation of memory for arousing events, they appear to do so through their influence on the activation or inhibition of NE in the amygdala (McGaugh 2000). Related data point to NE's role in fear conditioning to explicit and contextual stimuli.

Catecholaminergic neurons are capable of adjusting the level of transmitter synthesis and release depending on current demands and past history (Abercrombie and Zigmond 1995; Zigmond et al 1995). For example, when animals are exposed to repeated shock, dopamine β-hydroxylase activity, tyrosine hydroxylase, and synaptic levels of NE all increase (Irwin et al 1986; Karmarcy et al 1984; Melia et al 1991). Repeated exposure to stress also can increase responsivity of LC neurons to excitatory stimuli (Simson and Weiss 1994). As a result of these and other adaptations, repeatedly stressed animals may respond to future stressors with exaggerated catecholamine reactivity. These increased or "sensitized" responses generally follow exposure to novel and potentially threatening stressors (Zigmond et al 1995) and are likely related to exaggerated physiologic and behavioral reactivity (Southwick et al 1995).

In traumatized humans, there is accumulating evidence that a substantial proportion of those who develop PTSD also have hyperreactive noradrenergic systems. Evidence for sensitized noradrenergic systems in PTSD includes heightened physiologic responsivity to trauma-related cues (Orr 1997), elevated 24-hour urinary NE excretion (Yehuda et al 1992), increased 24-hour plasma NE (Yehuda et al 1998), increased cerebrospinal fluid (CSF) NE (Geracioti et al 2001), decreased platelet α-2 adrenergic receptor number (Perry et al 1990), and exaggerated subjective, behavioral, cardiovascular, and biochemical responses to yohimbine (Southwick et al 1993). Yohimbine is an α-2 adrenergic receptor antagonist that activates noradrenergic neurons by blocking the α-2 autoreceptor, thereby increasing presynaptic noradrenergic release. It also blocks postsynaptic α-2 receptors. The data suggest that exaggerated noradrenergic reactivity is related to a number of trauma-related symptoms including hypervigilance, exaggerated startle response, irritability, aggression, and intrusive memories (Southwick et al 1995).

Preventing Sensitization of Noradrenergic Systems

Preclinical and clinical investigations suggest a number of rational approaches that might be used to treat excessive arousal, exaggerated noradrenergic activity, and sensitization in the weeks following trauma. Locus coeruleus activity is regulated by a variety of neurotransmitters and neuropeptides with corticotropin-releasing factor (CRF) and glutamate having stimulatory effects and norepinephrine, epinephrine, neuropeptide Y (NPY), endogenous opiates, GABA, benzodiazepines, and serotonin, having inhibitory effects (Aghajanian et al 1977; Akaoka and Aston-Jones 1991; Aston-Jones et al 1994; Korf et al 1974; Simpson and Weiss 1994; Valentino et al 1991). Thus, yohimbine and piperozane (α-2 receptor antagonist that blocks the inhibitory effects of epinephrine and norepinephrine) increase the firing rate of the locus coeruleus with a resultant increase in NE release, whereas sympatholytics, NPY, opiates, benzodiazepines, and alcohol decrease LC firing and NE release (Charney et al 1995).

CATECHOLAMINES. To date, interventions designed to suppress noradrenergic hyperreactivity directly in trauma survivors with PTSD have been limited to open pharmacologic trials with the antiadrenergic agents clonidine (Kinzie and Leung 1989; Kolb et al 1984), guanfacine (Horrigan 1996), prazosin (Raskind et al 2002), and propranolol (Famularo et al 1990; Kolb et al 1984; Pitman 2002). Clonidine is an α-2 adrenergic agonist that suppresses release of NE through actions at the presynaptic autoreceptor. It also improves prefrontal cortical functioning through actions at the postsynaptic α-2 receptor, where it facilitates inhibition of irrelevant and distracting sensory stimuli, provides inhibitory feedback to the amygdala, and helps the organism to concentrate on the contents of working memory (Arnsten 1998). Clonidine has been reported as helpful for symptoms of hyperarousal, hypervigilance, sleep deprivation, exaggerated startle response, nightmares, irritability, and aggression in trials with combat veterans, Cambodian refugees, and children (Kinzie and Leung 1989; Kolb et al 1984; Perry et al 1990). Guanfacine, an α-2 adrenergic agonist with less sedating and hypotensive side effects than clonidine, appears to affect the same symptoms as clonidine (Horrigan 1996). Prazosin is an α-1 adrenergic receptor agonist that has been shown to reduce symptoms of PTSD especially nightmares in combat veterans with PTSD (Raskind et al 2002). Propranolol is a nonselective β-adrenergic blocking agent that affects B1 and B2 receptors. Open trials in children and combat veterans with PTSD have reported reductions in nightmares, explosiveness, exaggerated startle, and hyperalertness (Famularo et al 1990; Kolb et al 1984)

Although antiadrenergic agents have been recommended for the treatment of chronic PTSD, only one published trial has directly targeted the blockade of epinephrine and NE for the treatment of acute stress disorder (ASD) and prevention of PTSD. In a randomized double blind pilot study, Pitman et al (2002) administered propranolol 40 mg four times daily versus placebo to accident victims within 6 hours of the event. Treatment lasted for 10 days. Although PTSD symptom scores 1 and 3 months posttrauma did not differ significantly between the two groups, at 3 months the propranolol group demonstrated significantly less psychophysiologic reactivity (heart rate, skin conductance, corrugator electromyogram) to mental imagery that symbolized or resembled the index trauma. In a recent case report of a woman with PTSD in remission, Taylor and Cahill (2002) described the successful use of propranolol (within 48 hours of a new trauma) to treat reemergent symptoms of PTSD. These reports are consistent with data in healthy humans where Southwick et al (2002) found a positive association between enhanced noradrenergic activity and enhanced long-term memory and Cahill et al (1994) reported that propranolol blocked enhanced memory for an arousing story.

NEUROPEPTIDE Y. Neuropeptide Y (NPY) is a 36 amino acid neurotransmitter that is colocalized with NE in most sympathetic nerve terminals. It has been found in multiple stress responsive brain regions including the LC, amygdala, hippocampus, periaquaductal gray, and prefrontal cortex (Helig and Widerov 1995). In the peripheral and central nervous system, NPY inhibits release of the neurotransmitter with which it is colocalized. In numerous preclinical studies, NPY has been shown to inhibit firing rate of LC neurons and to inhibit release of NE through actions at the presynaptic Y2 receptor. Preclinical studies have shown that NPY inhibits firing rate of the locus coeruleus, inhibits release of CRF and NE, and is anxiolytic in a variety of animal models (Helig and Widerov 1995). An antistress effect of NPY also has been documented in healthy humans exposed to acute uncontrollable stress. In two separate investigations of NPY in military personnel during high-intensity training, Morgan et al (2000, 2001, 2002) reported a significant negative relationship between stress-induced release of NPY and stress-induced symptoms of dissociation as well as a positive association between NPY release and superior military performance during stress. Furthermore, in combat veterans with chronic PTSD, Rasmusson et al (2000) reported low baseline levels of NPY and a blunted NPY response to yohimbine.

Based on animal and human studies, one might speculate that individuals with reduced capacity for NPY modulation of NE would be at increased risk for developing PTSD symptoms when exposed to trauma. Because NPY reduces LC firing, reduces NE release, and is lower and less responsive in individuals suffering from PTSD, one might also hypothesize that early posttrauma administration of NPY would prevent sensitization of NE systems and related PTSD symptoms. To date no published reports describe the use of NPY in trauma survivors in order to prevent PTSD.

CRF. Corticotropin-releasing factor plays a critical role in the stress response and functions in a mutually reinforcing feedback loop with NE. For example, stress that activates NE neurons markedly increases CRF concentration in the LC (Chappel et al 1990); CRF infusion into the locus coeruleus increases firing rate of NE–LC neurons in a dose-dependent fashion, is anxiogenic, and produces significant increases in 3-methoxy-4-hydroxyphenylglycol (MHPG) in brain areas such as the amygdala and hypothalamus (Butler et al 1990). Furthermore, preclinical studies have demonstrated that chronic stress can cause hypersecretion of CRF (Coplan et al 1996). This evidence suggests that hypersecretion of CRF may serve as a modulating factor that enhances stress-related release of NE.

In humans, a large number of studies have reported abnormalities in hippocampal-pituitary-adrenal (HPA) axis functioning among trauma survivors with PTSD. The abnormalities have included alterations in 24-hour urine excretion, 24-hour plasma cortisol levels, lymphocyte glucocorticoid receptor number, cortisol response to dexamethasone, corticotropin (ACTH) response to CRF, and B-endorphin and ACTH response to metyrapone (Yehuda 2002). Additionally, two studies in combat veterans with chronic PTSD have reported elevated resting CSF levels of CRF (Baker 1999; Bremner 1997).

To date there are no published reports of pharmacologic interventions specifically targeting the HPA axis for the treatment of ASD or for the prevention of PTSD; however, based on the preclinical and clinical data discussed here, the use of CRF antagonists represents a rational approach to treat excessively aroused trauma survivors within the first few days or weeks of the event. Such trials are already in the planning stages.

OPIOIDS. Endogenous opiates, by decreasing activity of other stress-related neuromodulators such as CRF and NE, play an important counterregulatory role in the CNS. Preclinical investigations have shown that administration of morphine leads to hyperpolarization of u-opioid receptors on NE containing cells in the LC (Korf et al 1974). The result is reduced firing rate of the LC and reduced NE release. Opiates also inhibit neuronal activity in amygdala cells that respond to threat cues (Huang et al 1993). Additionally, administration of opiates immediately after a learning task impairs long-term memory by decreasing NE release in the amygdala, while administration of opiate antagonists enhances memory by increasing NE in the amygdala (McGaugh 1989, 2000). Taken together these data suggest that early use of opiates after a trauma might attenuate noradrenergic activity, block arousal enhanced consolidation of memory, and decrease the likelihood of developing a sensitized NE system with potentially related hyperarousal and reexperiencing symptoms.

Consistent with preclinical data, Saxe et al (2001) evaluated the effects of morphine administration on the development of PTSD in pediatric burn victims. Twenty-four children admitted to the hospital and receiving morphine for acute burn injuries were assessed for PTSD symptoms while in the hospital and 6 months after discharge. The authors found a significant negative association between amount of morphine administered and degree of PTSD symptomatology at the 6-month follow-up. No significant association was noted between PTSD symptoms and other types of medication prescribed to these children. Decrease in pain could not explain decrease in PTSD because no significant association was observed between symptoms of pain and PTSD outcome measures.

Further evidence that opiates can either dampen or prevent PTSD symptoms comes from studies in World War II and Vietnam veterans. Psychiatrists within the military system often used narcolepsy, a therapy designed to heavily sedate patients, for the treatment of WWII soldiers with battle fatigue. On the average, soldiers slept day and night for 1 week. By historical accounts, half of the sample awakened much improved and able to return to the battlefield, but the other half did poorly (Kolb 1991). In a study of Vietnam veterans with PTSD, Bremner et al (1996) found that subjects reported a dampening of hyperarousal symptoms in response to opiates, such as heroin.

BENZODIAZEPINES. GABA is the most prevalent inhibitory neurotransmitter in the brain. Benzodiazepines enhance the affinity of GABA recognition sites for GABA, thereby potentiating its inhibitory action. Animals exposed to uncontrollable stress develop a decrease in benzodiazepine receptor function in multiple brain regions, including the frontal cortex, involved in the stress response (reviewed in Bremner et al 1999). Pretreatment with benzodiazepines in animals that are exposed to uncontrollable stress blocks stress-related increases in NE turnover in the cortex, hypothalamus, hippocampus, amygdala, and LC (Drugan et al 1984; Grant et al 1980). Thus, stress-related decreases in benzodiazepine receptor function may play a role in the neurobiological and behavioral consequences of exaggerated noradrenergic activity. For example, decreased benzodiazepine receptor activity in the amygdala might result in increased noradrenergic activity and a resultant enhanced consolidation of stress-related memories and possibly an increase in intrusive recollections.

In a single photon emission computed tomography study of combat veterans with PTSD compared with healthy control subjects, Bremner et al (2000) reported a 41% lower distribution volume of [123] iomazenil binding in prefrontal cortex of the PTSD group. Because iomazenil is a benzodiazepine receptor antagonist that binds with high affinity and is used for the imaging of benzodiazepine receptors, these data are consistent with preclinical studies showing that animals exposed to inescapable stress exhibit reduced benzodiazepine receptors in the PFC (Lippa et al 1978; Wiezman et al 1989). This suggests that individuals with PTSD may have a similar decrease in benzodiazepine receptor binding and activation. These data raise the possibility that intrusive memories as well as disinhibited social and emotional behavior in veterans with chronic PTSD may be related to alterations in benzodiazepine receptor binding and resultant effects on other neurotransmitters such as NE. Consistent with this notion, Bremner et al (1996) found that PTSD patients specifically report improvement in intrusive and hyperarousal symptoms with benzodiazepines.

In the acute aftermath of trauma, benzodiazepines can reduce anxiety and arousal and improve sleep; however, prolonged use is not indicated. In a study of trauma survivors with an acute stress disorder (i.e., occurring 1–3 months after trauma), the short-term use of benzodiazepines for sleep was associated with an acute reduction in PTSD symptoms (Mellman et al 1998); however, another study found that early and more prolonged use of benzodiazepines was actually associated with higher rates of subsequent PTSD (Gelpin et al 1996). Finally, in a double-blind placebo-controlled study, the administration of the benzodiazepine alprazolam to individuals with PTSD failed to show any significant reduction in symptoms of PTSD (Braun et al 1990). Thus, at this time it is recommended that if benzodiazepines are used to treat extreme arousal, insomnia, and anxiety that their use be time limited. The relationship between the clinical phenomenon of worsening PTSD symptoms with chronic benzodiazepine use and the reduction in BDZ receptor binding in PTSD is not well understood. One possible explanation for a lack of improvement in PTSD symptoms within the context of chronic BDZ use is that such use reduces the ability of the patient to experience levels of arousal that are necessary for therapeutic extinction to occur (Walker and Davis 2002).

Dissociation and Cognitive Distortions

Individuals exposed to highly stressful events commonly experience alterations in their perceptual experience of themselves, their environment, and the passage of time. Although transient dissociative symptoms at the time of a trauma are not necessarily pathologic, in civilian accident victims (Shalev 2002), Vietnam veterans with PTSD (Bremner et al 1992; Marmar 1994), and survivors of disasters (Koopman et al 1994), peritraumatic dissociation has been associated with subsequent development of PTSD. Given the long-standing association between trauma, dissociation, and PTSD, excessive peritraumatic dissociation may represent a rational target for early pharmacologic intervention in symptomatic trauma survivors.

Recent investigations in healthy subjects have provided evidence that the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors plays a central role in symptoms of dissociation (Krystal et al 1995). In a series of studies conducted by Krystal and colleagues (Krystal et al 1995, 1999), administration of the NMDA receptor antagonist ketamine, which increases glutamate release through a facilitation of Na+, Ca++, and K+ channels, produced significant dose-dependent increases in dissociative symptoms. Low doses of ketamine caused alterations in the form and content of thought (such as paranoia, loosening of associations, tangentiality, and ideas of reference), whereas high doses caused dissociative symptoms commonly reported by trauma victims; such as slowed perception of time; tunnel vision; changes in intensity, shape, and color of the environment; alterations in body perception; and derealization (Krystal et al 1994). As predicted, pretreatment with a GABA agonist benzodiazepine before infusion with ketamine resulted in a significant reduction in some but not all dissociative symptoms (Krystal et al 1998). Pretreatment with haldol, an antipsychotic that blocks dopamine receptors, resulted in an improvement in ketamine-induced cognitive deficits but not in dissociative symptoms (Krystal et al 1999). Finally, pretreatment with lomotragine, an anticonvulsant that attenuates glutamate release via inhibition of sodium, calcium, and potassium channels, significantly decreased dissociative and cognitive effects of ketamine (Anand et al 2000).

The neurobiologic underpinnings of dissociation have also been studied in humans with PTSD using a variety of pharmacologic probes with differing mechanisms of action. Infusions of lactate (Rainey et al 1987), yohimbine (Southwick et al 1993), and meta-chlorophenylpiperazine (mCPP) (a 5-HT agonist with predominant effects on 5-HT2 and 5-HT1c receptors; Southwick et al 1997) have all been shown to induce pronounced symptoms of PTSD, anxiety and panic, and dissociation, including flashbacks, in combat veterans with PTSD. In healthy controls and patients with a variety of psychiatric disorders, yohimbine has commonly been used as a probe of noradrenergic responsivity and mCPP as a probe of serotonergic function. Although the precise mechanism of lactate induced anxiety and dissociation is not known, central noradrenergic stimulation has been suggested.

In a study of combat veterans and healthy control subjects who received either intravenous (IV) yohimbine or saline solution on two test days in a double-blind randomized balanced-order design, Southwick et al (1993) reported a high rate of anxiety and panic, PTSD-specific symptoms, and dissociative symptoms among the PTSD patients in response to yohimbine but not placebo. A broad spectrum of dissociative symptoms were reported including derealization, depersonalization, and full-blown flashbacks. In a separate study comparing the effects of IV yohimbine, mCPP, and saline solution in combat veterans with PTSD compared with control subjects, the PTSD group experienced marked symptoms of PTSD, anxiety and panic, and dissociation in response to both yohimbine and mCPP but not placebo (Southwick et al 1997). Some veterans had greater behavioral, physiologic, and biochemical responses to yohimbine, whereas others had more roboust responses to mCPP. In general, patients tended to experience panic attacks and flashbacks following yohimbine or mCPP but not both medications. Finally, like yohimbine and mCPP, infusion of IV lactate has been shown to induce pronounced PTSD symptoms, anxiety, panic, and dissociative symptoms in Vietnam combat veterans with PTSD.

The finding that multiple pharmacologic agents with different mechanisms of action are each capable of inducing dissociative symptoms in individuals with PTSD suggests that these agents may not directly induce dissociation but instead contribute to activation of networks that lead to dissociation in vulnerable individuals. It is likely that these agents disturb cortical integration at multiple levels. Pyramidal neurons, which use glutamate as their primary neurotransmitter, are the key output neurons of the cortex. These pyramidal neurons are regulated locally by GABAergic neurons and from a distance by subcortical monoaminergic, glutamatergic, and peptidergic systems. Activity of glutamatergic neurons in the amygdala, hippocampus, and thalamus is also modulated by multiple neurobiologic inputs, including those from noradrenergic and serotonergic systems (Chambers et al 1999; Krystal et al 1995). For example, it has recently been reported that 5-HT, by activating GABA interneurons, can modulate glutamatergic inputs to the amygdala (Stutzmann and LeDoux 1999). Furthermore, the ability of 5-HT to modulate glutamateric activity is dependent on the presence of corticosterone (Stutzmann and LeDoux 1998). Although multiple complex, neurobiologic perturbations can lead to dissociation, it is likely that the final common pathway involves an imbalance of excitatory and inhibitory processes related to glutamatergic transmission with a resultant compromise in coherent exchange of information within corticolimbic networks.

Treatment of Dissociation

Because dissociation may be caused by alterations in a number of stress-related neurobiologic systems, it is probable that multiple pharmacologic interventions could potentially affect symptoms of dissociation (Chambers et al

1999). For example, attenuating the release of monoamines and thereby diminishing exaggerated glutamatergic activity would be one rational approach to treating dissociation. Thus, therapies discussed earlier for the treatment of adrenergic hyperresponsivity such as propranolol, clonidine, and guanfacine might lessen the likelihood that a traumatized individual would experience symptoms of arousal and dissociation (Chambers et al 1999; Southwick et al 1999).

A second approach might involve restoring deficient inhibitory mechanisms via endogenous opiate or GABAergic systems (Chambers et al 1999). Although benzodiazepines and opiates are not specifically recommended for the long-term treatment of PTSD, it is possible that these agents would lessen the frequency and intensity of dissociative symptoms in trauma survivors. Similarly, selective serotonin reuptake inhibitors, through their effects on serotonin, might dampen glutamatergic activity via effects on GABAergic interneurons.

Third, attenuation of excess glutamate might represent the most direct approach to treating dissociative symptoms in trauma survivors (Chambers et al 1999). As noted earlier, the NMDA receptor agonist lomotragine acts by decreasing presynaptic release of glutamate and has been shown to attenuate dissociative, perceptual, and cognitive distortions in healthy subjects who have been administered ketamine. It is also possible that early treatment with lomotrogine would decrease the likelihood of establishing intrusive traumatic memories and long-standing sensitization of emotional responses. Glutamate is considered essential to CNS mechanisms of plasticity including those related to learning and memory. The long-lasting effects of extreme uncontrollable stress and trauma on neural structures and function may well involve processes involving changes in neuronal interconnectivity and which may be dependent on changes in glutamatergic transmission. Lomotrogine and other NMDA blocking agents might decrease glutamatergic transmission and thereby affect mechanisms involved in the formation and maintainance of traumatic memories and of clinically significant emotional responses to stress. In animals NMDA antagonists have been shown to prevent initiation of a process called long-term potentiation (LTP; a neural process representing learning) and disrupt the acquisition of conditioned fear (Campeau et al 1992). Furthermore, it is possible that early treatment with agents such as lamotrogine might protect trauma survivors from possible glutamate-related neural injury. Glutamate-related injury to hippocampal neurons has been suggested as a possible consequence of extreme trauma in survivors with PTSD (Chambers et al 1999; Krystal et al 1995). The degree to which other mood stabilizers may or may not affect dissociation awaits future study.

A note of caution is warranted. Recent work on the neural basis of extinction (for full review, see Davis and Myers 2002) has provided robust evidence that extinction is an active learning process in which both glutamate and GABA play a critical role. Davis and Myers cautioned that the development of plasticity that is associated with extinction depends not on GABA but on excitatory neurotransmitters such as glutamate.

> The available data support the view that it is likely that extinction is associated with a strengthening of connections between the sensory pathways transmitting conditioned stimulus related information and a population of GABAergic cells that mediate extinction performance. Thus, GABA release during extinction training would be expected to hinder extinction because the development of neural plasticity requires significant excitation of target cells. (Davis and Myers 2002, p. 1004)

Thus, it is possible that a premature effort on the part of clinicians to "help" trauma survivors through the early administration of pharmacologic agents that modulate GABA and glutamate transmission may not have a beneficial effect but rather prevent these individuals from developing the learning process of extinction (or the learning of safety cues) and retard their recovery process.

Summary

In this report, we have focused on neurobiologic underpinnings of trauma-induced excessive levels of arousal and dissociation, two symptom clusters that have been shown to predict later development of PTSD. We have largely limited our discussion to noradrenergic and glutamatergic systems because these have been the most extensively studied neurobiologic systems in humans who are experiencing symptoms of dissociation and stress-induced arousal. Clearly, dissociation and arousal are extremely complex and involve the interplay of multiple brain regions and neurotransmitter systems.

It has been suggested that repeated bouts of excessive arousal and dissociation increase the likelihood that stress-related neurobiological systems (e.g., noradrenergic and glutamatergic systems) become sensitized. It is generally believed that once these systems are sensitized, treatment is more difficult and probably less successful. Thus, early intervention with highly symptomatic individuals is of utmost importance.

Reducing arousal may require psychosocial or pharmacologic approaches, or both. Initially, efforts must be made to reduce exposure to ongoing stressors by removing the survivor from exposure to further trauma, by avoiding secondary stressors (such as untreated physical pain, unsettling police interrogations, prolonged separation from loved ones, and uncertain living arrangements) and by recognizing and minimizing traumatic reminders that may trigger intrusive memories and repeated episodes of excessive arousal and dissociation (Shalev 2002).

To date there is almost no empirical data on the use of pharmacologic agents for the treatment of acute reactions to trauma and ASD. Nevertheless, many clinicians and researchers recommend the short-term use of pharmacologic agents to reduce excess arousal when other approaches such as relaxation, increased family and social support, brief cognitive–behavioral therapy, and psychological debriefing have failed. It is important to note that if a specific therapy increases arousal at or near the time of trauma, as has been reported with some types of debriefing, that therapy is probably contraindicated. Rational pharmacologic approaches to treating excess arousal include the short-term use of propranolol, clonidine, or guanfacine. The short-term use of benzodiazepine anxiolytics and hypnotics may also prove helpful for pronounced insomnia and anxiety.

Although we have not specifically addressed trauma-induced depression, Freedman et al (1999) have reported that high levels of depressive symptoms 1 and 5 weeks after trauma predict the development of chronic PTSD. It is possible that the use of antidepressants in trauma survivors with prominent depressive symptoms may help with mood-related symptoms and possibly decrease the likelihood of developing PTSD. Preclinical studies have shown that pretreatment with antidepressants protects animals from many of the maladaptive behavioral and neurobiological consequences of uncontrollable stress (Duman et al 2001).

To date there has been only one published report on the use of antidepressants for ASD. In recently traumatized children, Robert et al (1999) treated subjects meeting criteria for acute stress disorder with either imipramine or chloral hydrate for a period of 2 weeks. Those treated with imipramine experienced significantly greater reductions in symptoms of acute stress disorder than those treated with chloral hydrate. Although this study was of insufficient length to evaluate tricyclic efficacy for preventing PTSD, the results did suggest that tricyclics may be effective in reducing excessive arousal.

Future directions in pharmacologic research call for controlled trials of antiadrenergics and anxiolytics for the treatment of ASD. Controlled trials are essential given the limited information in this field. Other rational approaches include controlled trials of antidepressants, CRF antagonists, NPY, GABAergic anticonvulsants such as valproate, and possibly NMDA antagonists such as lomotragine (Hertzberg et al 1999).

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